REMARKS/ARGUMENTS

The Status of the Claims.

Claims 1, 3-15, 34-44 and 53-67 are pending with entry of this amendment, claims 1, 4 and 63 being amended herein. These amendments introduce no new matter and support is replete throughout the specification. These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record.

With respect to claim 1, support for isolated, synthesized and recombinant antibodies can be found throughout the specification. For example, see specification at page 20, lines 24-30; page 26, lines 2-8 and lines 10-12; page 27, lines 4-32; page 47, lines 9-13; page 46, lines 22-31; page 47, lines 9-10; and Table 1 (pages 59-60).

With respect to claims 4 and 63, the informalities helpfully pointed out by the Examiner have been corrected.

Applicants submit that no new matter has been added to the application by way of the above Amendment. Accordingly, entry of the Amendment is respectfully requested.

The Information Disclosure Statement.

Applicants note with appreciation the Examiner's thorough consideration of the references cited in the Information Disclosure Statement (Form 1449) submitted on August 5, 2004.

35 U.S.C. §112, First Paragraph

Claims 3-13, 39-42 and 61-63 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not being enabled ("The specification has not taught how to make antibodies as broadly defined by the claims") and as allegedly requiring undue experimentation to produce the claimed invention.

The Office Action indicates that the 112, first paragraph rejection has been maintained with respect to antibodies with less than a full set of CDRs from SEQ ID NOS: 1 and 2, antibodies with conservative substitutions in the CDRs as well as frameworks,

antibodies with CDRs having at least 70% sequence identity as compared to the CDRs of SEQ ID NO: 1 and 2, and antibodies in which the V_H or V_L of SEQ ID NO 1 or 2 replaced with a human V_H or V_L. The Action also alleges that antibodies as defined by the claims would not bind antigen, that "it is unpredictable which CDRs and frameworks (one or two in each chain as defined by the claims) to substitute or which residues to maintain to obtain the required binding," and that "again, it is unpredictable which if any human V_H or V_L would be able to pair with the V_H or V_L of SEQ ID NO: 1 or 2 and produce a binding antibody as well as internalize." Furthermore, the Office Action alleges that "even very conservative substitutions can abolish the binding of an antibody..." and that "even conservative substitutions are unpredictable as far as obtaining antigen binding antibodies are concerned. Therefore it would require undue experimentation to produce the claimed invention." Applicants traverse.

The specification is enabling

To be an enabling disclosure under 35 U.S.C. §112, first paragraph, a patent must contain a description that enables one skilled in the art to make and use the claimed invention. That some experimentation is necessary does not constitute a lack of enablement; the amount of experimentation, however, must not be unduly extensive. *See* In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Applicants submit that the specification does in fact provide more than adequate description, as required under §112, to enable one of skill in the art to make and use the claimed invention. The specification provides considerable guidance as to how one of skill can prepare antibodies of the claimed invention (see, for example, page 13, lines 19-23; page 20, line 24 through page 31, line 2; and in the examples). Furthermore, the specification provides numerous techniques that can be employed for recognizing and/or selecting the prepared antibodies (see, for example, page 31, line 4 through page 36, line 31 and within Examples 1-3).

Experimentation with respect to Inoperable Embodiments

The Office's rejection under §112, first paragraph, appears to be more concerned with the presence of inoperable embodiments, and alleged undue experimentation, than with the extent of written description provided in the specification. As note in Wands,

"The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. The test is not merely quantitative, since *a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance* with respect to the direction in which the experimentation should proceed" (emphasis added). Applicants submit that the specification provides considerable guidance, as noted herein, with respect to both synthesis and selection of the internalizing antibodies of the claimed invention. Furthermore, given the current availability of a number of immunoassay formats as well as a multitude of platforms for high through-put screening, microscale analyses, and the like, Applicants submit that the experimentation involved in testing a series of putative antibody sequences for epitope binding and internalization is routine to one of skill in the art.

As a further point, Applicants wish to point out that a claim may properly read upon both operative and inoperative embodiments, and still be patentable. *See*, for example, In re Cook and Merigold, 439 F.2d 730, 169 U.S.P.Q. 298 (C.C.P.A. 1971) ("The mere possibility of inclusion of inoperative subject matter does not prevent allowance of broad claims.") In re Dinh-Nguyen and Stenhagen, 181 USPQ 46 (CCPA 1974) also notes "It is not the function of claims to specifically exclude either possible inoperative substances or ineffective reactant proportions."

One of skill can readily ascertain operative from inoperative embodiments of the claims

Enablement of a claim generally relates to whether the claim can be practiced without undue experimentation, a test that can be informed by a consideration of (1) whether there are a substantial number of inoperable embodiments that a claim can be read upon, and (2) whether one of skill can readily ascertain operative from inoperative embodiments. See, for example, In re Cook and Merigold, *supra*; Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 224 USPQ 409 (Fed Cir. 1984); Crown Operations International Ltd. V. Solutia Inc. 62 USPQ2d 1921, 1925 (Fed. Cir. 1999); and Process Control Corp. v. HydReclaim Corp. 52 USPQ2d 1029.

Applicants note that antibodies have been the subject of several decades of research, and as a result, the general structure of immunoglobulins and the functions of

various antibody domains is well within the understanding of one of skill. The literature suggests that thousands of antibody genes from a variety of organisms have been sequenced, and numerous immunoglobulin constructs and/or artificial antibodies have been generated, both in mammals and in cell culture. Thus, it is possible to make and easily screen millions if not billions, of different antibodies for a desired property, simultaneously, using widely available antibody library technologies and array technologies. In the present case, the specification also provides considerable guidance as to how one of skill can prepare antibodies of the claimed invention (see, for example, page 13, lines 19-23; page 20, line 24 through page 31, line 2; and in the examples). These methodologies include preparation by solid phase chemical synthesis (page 21), recombinant expression (pages 21-25), *ex vivo* production using, for example, a phage display library (pages 25-28); chain shuffling (page 28), site-directed mutagenesis (page 29), and CDR randomization (pages 29-30).

The methodologies provided in the specification can, of course, be directed to generate both operative and inoperative embodiments. It is not a requirement that the claims only encompass operable embodiments. As noted in Ex parte Cole, 223 USPQ 94 (BPAI 1983), "It is always possible to theorize some combination of circumstances which would render a claimed composition or method inoperative, but the art-skilled would assuredly not choose such a combination." Thus, Applicants submit that one of skill in the art could readily avoid many putatively inoperable embodiments through judicial planning and experimental design.

Furthermore, one of skill is readily able to differentiate between operative and inoperative embodiments. In the present case, the specification provides considerable guidance with respect to identification of claimed antibodies. For example, numerous techniques that can be employed for recognizing and/or selecting antibodies of the claimed invention, including methods for determination of K_d, competition studies, cross-reactivity with anti-idiotypic antibodies, cross-reactivity studies with F5 and/or C1, and internalization assays, are provided in the specification at, for example, page 31, line 4 through page 36, line 31 and within Examples 1-3. Furthermore, methods for determination of sequence identity are provided at, for example, page 9, line 27 through page 12, line 3. Given the teachings of the specification and the truly vast array of available literature regarding antibody

construction, it is reasonable to conclude that one of skill can readily identify operative embodiments (e.g., internalizing antibodies that bind to the c-rbB2 epitope recognized by F5 and C1) from inoperative embodiments (e.g., non-binding or non-internalizing antibodies).

The use of "open language" in the claims

According to the Office Action, the prior art teaches that antibodies that do not have a full set of CDRs from the light and heavy chains of a specific antibody do not bind antigen. Based upon previous conversations with the Examiner, this portion of the rejection appears to be in response to claims drawn toward antibodies "comprising a CDR of SEQ ID NO:1" (or SEQ ID NO:2), or "comprising at least two CDRs" of SEQ ID NO:1 or SEQ ID NO:2, and claims drawn to chimeric molecules including these antibodies. Applicants respectfully note that the "comprising" language employed in the claims is open language and thus does not exclude the presence of additional CDRs. Rather, the use of the term "comprising" indicates that the claimed antibody includes at least one (or more) CDR from the provided sequences. Such language is, of course, universally accepted "open" claim language (see, for example, *Ex parte David and Tuukanen*, 80USPQ 448, 450 (PO Bd. App. 1949), in which the term "comprising" is defined). While one of skill in the art would probably not prepare antibody sequences having less than the desired number of CDRs (based upon a general understanding of the mechanism of action of antibody:antigen interaction), such antibody derivatives could readily be prepared and screened for epitope binding and internalization, using the methods provided in the specification. As noted above, given the extent of technological innovation in biotechnology over the 15+ years since the *Wands* decision, the experimentation involved in testing putative antibody sequences for F5/C1 epitope binding and internalization is routine and does *not* require undue experimentation.

Applicants submit that claims 3-13, 39-42 and 61-63 are enabled by the specification, per the requirements of 35 U.S.C. §112, first paragraph, and respectfully request that the rejection be withdrawn.

35 U.S.C. § 101.

Claims 1, 3-13, 39-42, 55, and 67 were newly rejected under 35 U.S.C. § 101, as allegedly directed to non-statutory subject matter. Applicants have amended the claims as

helpfully suggested by the Examiner, and respectfully request that the rejection be withdrawn.

35 U.S.C. §103(a)

THE CLAIMS ARE PATENTABLE OVER XU, BIRD AND CHAUDHARY

Claims 1, 34-38, 53-54 and newly added claims 55-57, 59-60 and 67 under 35 U.S.C. §103(a) have been rejected as allegedly unpatentable over Xu et al. (Int. J. Cancer 53:401-408, 1993) and further in view of Bird et al. (Science 242:423-426, 1988). Applicants traverse.

Three requirements must be met for a *prima facie* case of obviousness, the first of which is that the prior art reference teach all of the limitations of the claims (M.P.E.P § 2143.03). The claims are drawn to internalizing antibodies that specifically bind to an epitope of the c-erbB2 receptor (which epitope is defined by its ability to binds to sequences F5 or C1, e.g., SEQ ID NO:1 or SEQ ID NO:2), as well as chimeric molecules and compositions comprising these antibodies. Xu is alleged to teach or describe internalizing antibodies capable of binding to c-erbB2 receptor. Bird and Chaudhary are alleged to teach methods for preparation of single chain antibodies. However, the cited publications (alone or in combination) do not teach or disclose internalizing antibodies that bind to the epitope recognized by F5 and C1.

The Office Action alleges that "it is still not clear if there is a difference in binding between the Xu antibodies and C1 or F5" (page 5, lines 12-13). Applicants respectfully submit the following further clarification regarding the assertion that the epitope recognized by C1 and F5 is different from that recognized by the antibodies employed by Xu. As noted in the declaration (paragraph V), F5 and C1 antibodies recognize the same epitope. Data generated using SKBr-3 cells and monovalent and bivalent forms of F5 indicate that approximately 80% of antibody is internalized by as early as 2 hours incubation at 37°C (see Figure 1 on page 276 of Neve 2001 Biochem. Biophys. Res. Comm. 280:274-279). In stark contrast, as noted previously (paragraph IX of the declaration), the internalization efficiency determined after a one hour incubation for Xu antibodies TA1 and ID5 is 30% and 27%, respectively. Furthermore, according to Xu, the other antibodies examined in the studies

were internalized at similar rates (page 406, second column). While the internalization periods are not identical (1 hour versus 2 hours), the above-cited data plainly indicate that the F5 antibodies are internalized at a different rate that the Xu antibodies.

It is worth noting that the Office bears the burden of proof in establishing that the alleged prior art antibodies are the same as that which is being claimed, rather than Applicants proving that they are different. Nevertheless, in the present case, Applicants have attempted to further prosecution by providing an expert declaration showing that the antibodies of the prior art have physical properties that differ from those of the invention, and are, therefore, not relevant to the subject claims. The Office is not free to dismiss this expert opinion and the clear evidence of physical difference with an *ad hoc* argument that the physical evidence could be an artifact of the experiment used. Instead, the Office must accept the most likely interpretation of the evidence. At this point, there is no evidence whatsoever that the prior art antibodies bind the epitope recognized by F5 and C1 as required by the claims. However, there is clear evidence that the prior art antibodies have properties that are entirely different from such antibodies. An expert has stated that one of skill would draw the conclusion that the prior art antibodies bind a different epitope than that bound by F5 and C1. Applicants have clearly established by a preponderance of evidence that the prior art antibodies are different. As such, the rejection is improper and should be withdrawn.

The Xu publication does not teach or describe the limitation of the claimed invention, e.g., an internalizing antibody that recognizes the F5/C1-binding epitope of c-erbB2 receptor. Neither Bird nor Chaudhary remedy this deficit. Applicants respectfully submit that the claimed invention is not rendered unpatentable over Xu et al. further in view of Bird et al. and Chaudhary et al. because the cited references do not teach the limitations of the claims. Applicants respectfully submit that this rejection is improper and should be withdrawn.

THE CLAIMS ARE PATENTABLE OVER SHAWVER, BIRD AND CHAUDHARY

Claims 1, 34-38, 53-54 and newly added claims 55-57, 59-60 and 67 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Shawver et al. (Cancer Res. 54:1367-1373, 1994) and further in view of Bird et al. (Science 242:423-426, 1988) and Chaudhary et al. (PNAS 87:1066-1070, 1990). Applicants traverse.

As noted above, the claims are drawn to internalizing antibodies that specifically bind to an epitope of the c-erbB2 receptor (which epitope is defined by its ability to binds to sequences F5 or C1, e.g., SEQ ID NO:1 or SEQ ID NO:2), as well as chimeric molecules and compositions comprising these antibodies. Shawver is alleged to teach or describe internalizing antibodies capable of binding to c-erbB2 receptor. Bird and Chaudhary are alleged to teach methods for preparation of single chain antibodies. However, the cited publications (alone or in combination) do not teach or disclose internalizing antibodies that bind to the epitope recognized by F5 and C1.

The Office Action alleges that "it is still not clear if there is a difference in binding between the Shawver antibodies and C1 or F5" (page 6, lines 18-19). Applicants respectfully submit the following clarification of the assertion that the epitope recognized by C1 and F5 is different from that recognized by the antibodies employed by Shawver. As noted above, F5 and C1 antibodies recognize the same epitope, approximately 80% of which is internalized after 2 hours incubation of SKBr-3 cells with F5 at 37°C (see Figure 1 of Neve et al., *supra*). However, only 28% of the Shawver antibodies are internalized after 3 hours incubation (paragraph X of the declaration). Thus, the above-cited data indicate that the F5 antibodies are internalized at a much faster rate that the Shawver antibodies.

As noted above, the Office bears the burden of proof in establishing that the alleged prior art antibodies are the same as that which is being claimed. Applicants have provided an expert declaration showing that the antibodies of the prior art have physical properties that differ from those of the invention, and are, therefore, not relevant to the subject claims. The Office is not free to dismiss this expert opinion and the clear evidence of physical difference with an *ad hoc* argument that the physical evidence could be an artifact of the experiment used. Instead, the Office must accept the most likely interpretation of the evidence. Since there is no evidence whatsoever that the prior art antibodies bind the epitope recognized by F5 and C1 as required by the claims, there is clear evidence that the prior art antibodies have properties that are entirely different from such antibodies, and an expert in the field has stated that one of skill would conclude, based upon available experimental evidence, that the prior art antibodies bind a different epitope than that bound by F5 and C1,

Applicants have clearly established by a preponderance of evidence that the prior art antibodies are different. As such, the rejection is improper and should be withdrawn.

The Shawver publication does not teach or describe the limitation of the claimed invention, e.g., an internalizing antibody that binds to the epitope recognized by F5 and C1. Neither Bird nor Chaudhary remedy this deficit. Applicants respectfully submit that the claimed invention is not rendered unpatentable over Shawver et al. further in view of Bird et al. and Chaudhary et al. because the cited references do not teach the limitations of the claims. Applicants respectfully submit that this rejection is improper and should be withdrawn.

THE CLAIMS ARE PATENTABLE OVER SHAWVER, BIRD, CHAUDHARY, AND SCHIER

Claims 1, 34-38, 53-60, and 63-67 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Shawver et al. and further in view of Bird et al., Chaudhary et al., and Schier et al. (J. Mol. Biol. 255:28-43, 1996). Applicants traverse.

As noted above, Applicants submit that the claimed invention is not rendered unpatentable over Shawver, Bird and Chaudhary, alone or in combination, because the cited references do not teach internalizing antibodies that bind to the epitope recognized by F5 and C1. Schier is alleged to teach affinity driven selection in phage; however, Schier does not teach or disclose internalizing antibodies that bind to the epitope recognized by F5 and C1. Since the cited art does not teach or disclose the limitations of the claimed invention, Applicants respectfully submit that this rejection is improper and should be withdrawn.

THE CLAIMS ARE PATENTABLE OVER XU, BIRD, CHAUDHARY AND SCHIER

Claims 1, 34-38, 53-60, 62, and 63-67 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Xu et al. and further in view of Bird et al., Chaudhary et al., and Schier et al.. Applicants traverse.

As noted above, Applicants submit that the claimed invention is not rendered unpatentable over Xu, Bird and Chaudhary, alone or in combination, because the cited references do not teach internalizing antibodies that bind to the epitope recognized by F5 and C1. Schier is alleged to teach affinity driven selection in phage; however, Schier does not teach or disclose internalizing antibodies that bind to the epitope recognized by F5 and C1.

Since the cited art does not teach or disclose the limitations of the claimed invention, Applicants respectfully submit that this rejection is improper and should be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, a telephone interview with the Examiner is hereby requested. Please telephone the undersigned at (510) 769-3511 to schedule an interview.

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Respectfully submitted,

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Attachments:

1) A transmittal sheet;
2) A fee transmittal sheet; and,
3) A receipt indication postcard.

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